ISSUES IN THE ANALYSIS OF ENVIRONMENTAL ENDOCRINE DISRUPTORS

Monday, March 27, 2000

American Chemical Society National Meeting

San Francisco, CA

Pharmaceuticals and Personal Care Products in the Environment — An Emerging Concern

Organizers: **L.H. Keith**
L.L. Needham
T.L. Jones-Lepp

Go to Afternoon Session

Presiding: **C.G. Daughton**
T.A. Ternes

Time	Paper
8:30 a.m.	Introductory remarks.
8:40 a.m.	**Pharmaceuticals in the environment — overarching issues and concerns.** C.G. Daughton
9:00 a.m.	**Pharmaceuticals and metabolites as contaminants of the aquatic environment — an overview.** T. Ternes
9:20 a.m.	**Drugs in sewage treatment plant effluents in Canada.** C. Metcalfe, B. Koenig, T. Ternes and R. Hirsch
9:40 a.m.	**Fate of fluoroquinolone antibiotics during municipal wastewater treatment.** A.C. Alder, E. Golet, S. Ibric and W. Giger
10:00 a.m.	**Occurrence of macrolide and sulfonamide antibiotics in the aquatic environment of Switzerland.** N.S. Nipales, C.S. McArdell, E. Molnar and W. Giger
10:20 a.m.	Break
10:35 a.m.	**Occurrence of antibiotics in surface and ground water near confined animal feeding operations and waste water treatment plants using radioimmunoassay and liquid chromatography/electrospray mass spectrometry.** M. Meyer, D.W. Kolpin, J.E. Bumgarner, J.L. Varns and J.V. Daughtridge

10:55 a.m. **Occurrence of pharmaceutical residues in sewage, river, ground and drinking water in Greece and Germany.** T. Heberer, B. Fuhrmann, K. Schmidt-Bäumler, D. Tsipi, V. Koutsouba and A. Hiskia

11:15 a.m. **Occurrence of phenazone analgesics in landfill-leachate polluted groundwater.** M. Ahel and I. Jelicic

11:35 a.m. **Occurrence and fate of synthetic musks in the aquatic system of urban areas: Polycyclic and nitro musks as environmental pollutants in surface waters, sediments and biota.** T. Heberer and A. These

ABSTRACTS

Pharmaceuticals in the environment — overarching issues and concerns.
Christian G. Daughton. Environmental Chemistry Branch, Environmental Sciences Division, U.S. Environmental Protection Agency, ORD/NERL, 944 East Harmon Ave, Las Vegas, NV 89119, fax: 702-798-2142, daughton.christian@epamail.epa.gov.

Certain pharmaceutically active compounds (e.g., caffeine, aspirin, and sex steroids) have been known for over 20 years to enter the environment by a variety of routes - primarily via treated and untreated sewage effluent. Only more recently has a larger picture emerged - where it is evident that numerous drugs and personal care products from a wide spectrum of therapeutic and consumer-use classes, many having potent biochemical activity, can occur in the environment (albeit at very low concentrations), especially in natural surface and ground waters. The full extent, magnitude, and ramifications of their presence in the aquatic environment are largely unknown. Whether pharmaceuticals and personal care products in the environment pose an exposure risk to humans or wildlife is not known. Aquatic exposures are noteworthy, however, in that they can be continuous. Nearly all ecological monitoring studies to date have been performed in Europe. While the (over)use and subsequent direct and indirect release of antibiotics and natural/synthetic steroids to the environment has generated nearly all the controversy to date regarding pharmaceuticals as pollutants, a plethora of other drug classes, bioactive metabolites and transformation products, as well as personal care products have yet to be examined. This paper will summarize a number of issues not frequently encountered in discussions of environmental toxicology and which deserve further attention and debate.

Notice: The U.S. Environmental Protection Agency (EPA), through its Office of Research and Development (ORD), funded this research and approved this abstract as a basis for an oral presentation. The actual presentation has not been peer reviewed by EPA.

Pharmaceuticals and metabolites as contaminants of the aquatic environment — an overview. Thomas Ternes. ESWE-Institute for Water Research and Water Technology, Soehnleinstrasse 158, Wiesbaden C-65201 Germany, fax: 49-611-7804375, thomas.temes@stadtwerke-wiesbaden.de.

While tons of individual pharmaceuticals have been used yearly in various countries over the last few decades, few investigations have been published about the assessment of their environmental relevance - a result of their inadvertent discharge from sewage treatment and land run-off. In Germany for instance, up to 100 t of individual drugs are prescribed every year. In our laboratory, analytical procedures were elaborated for a total of 84 analytes, enabling the simultaneous determination of polar drug residues belonging to different medicinal classes, such as lipid regulators, antibiotics, and estrogens in both sewage treatment plant (STP) effluent and drinking water. In a search for target analytes, 36 of 55 pharmaceuticals and 5 of 9 metabolites were quantified in at least one STP effluent. In general, the removal rates in the investigated municipal STP exceeded 60 %. The highest concentrations of drug residues were measured for the antiepileptic carbamazepine, with a maximum of 6.3 µg/L. X-ray contrast media were found in concentrations as high as 15 µg/L (iopamidol) and 11 µg/L (iopromide). In 40 German rivers and streams, 31 pharmaceuticals and five metabolites were quantified in at least one sample. Highest median values were detected for bezafibrate (0.35 µg/L) and carbamazepine (0.25 µg/L), Frequently, in small rivers and streams, much higher concentrations were detected than in big rivers like the Rhine or Main. In groundwater samples taken close to stream banks, sometimes relatively high concentrations of pharmaceuticals (up to 2.4 µg/L) were detected. In drinking water, only 9 of 65 target pharmaceuticals were found, and then, always in the lower ng/L-range.

Drugs in sewage treatment plant effluents in Canada. Chris Metcalfe[1], Brenda Koenig[1], Thomas Ternes[2] and Roman Hirsch[2]. [1]Environmental and Resource Studies, Trent University, Peterborough, ON K9J 7B8, Canada, fax: 705-748-1569, cmetcalfe@trentu.ca; [2]ESWE-Institute for Water Research and Water Technology, Soehnleinstrasse 158, Wiesbaden, C-65201, Germany.

Final and raw (untreated) effluent samples from 10 sewage treatment plants (STPs) in Canada were analyzed for residues of several prescription and non-prescription drugs. A large number of neutral and acidic drugs were detected in STP effluents, including antiphlogistics, lipid-regulating agents, and antiepileptic drugs. Residues were extracted from effluents by solid phase extraction, followed by either methylation and GC-MS analysis in the case of acidic drugs, or direct analysis of neutral drugs by LC-ESI-MS-MS. Lipid-regulating agents such as Bezafibrate and their metabolites were detected in most effluents at ng/L concentrations and antiphlogistics such as Indomethecine, Ibuprofen, and acetylsalicyclic acid and its metabolite (i.e., salicylic acid) were also detected at ng/L concentrations. The antiepileptic neutral drug, Carbamazepine was detected in almost all samples at concentrations as high as 2

µg/L. The widespread occurrence of Carbamazepine may be explained by use of this drug for other therapeutic purposes besides treatment of epilepsy. Comparisons between raw and final effluent samples indicated that concentrations of some drugs declined through the sewage treatment process but others (i.e., Carbamazepine) were relatively resistant to degradation. Drug residues in surface waters near discharges from STPs may affect the health of aquatic organisms. Preliminary toxicity data with rainbow trout indicate that lipid-regulating agents (i.e., Bezafibrate) can reduce serum cholesterol levels in fish. Further data are needed on the distribution of these drugs in surface water and ground water in North America.

Fate of fluoroquinolone antibiotics during municipal wastewater treatment. Alfredo C. Alder, Eva Golet, Slavica Ibric and Walter Giger. Swiss Federal Institute for Environmental Science and Technology (EAWAG) and Swiss Federal Institute of Technology (ETH), Ueberlandstrasse 133, PO Box 611, Dübendorf, CH-8600, Switzerland, fax: 41-1-823-5028, alder@eawag.ch.

Our motivation for studying the fate of antibiotics in the aquatic environment arises whether trace concentrations may contribute to the increasing resistance of microorganisms towards antibiotics. Fluoroquinolone (FQ) antibiotics, are liscensed for the use in human and veterinary medicine. This contribution reports on field studies following the input of FQs in surface waters. Daily variations of the concentrations in primary and secondary effluents were studied to determine elimination rates in the aqueous phase.The leading FQ in human medicinal use, Ciprofloxacin, was measured in concentrations of 70-80 ng/l in 24 h composite samples of the effluent of a municipal wastewater treatment plant (WWTP). These investigations show that Ciprofloxacin is eliminated to 70-80 % in this WWTP and can reach surface waters. For an exposure assesment of these antibiotics, the environmental fate of other FQs are also studied.

Occurrence of macrolide and sulfonamide antibiotics in the aquatic environment of Switzerland. Norriel S. Nipales, Christa S. McArdell, Eva Molnar and Walter Giger. Swiss Federal Institute for Environmental Science and Technology (EAWAG) and Swiss Federal Institute of Technology, (ETH), Ueberlandstrasse 133, PO Box 611, Dübendorf, CH-8600, Switzerland, fax: 41-1-823-5028, mcardell@eawag.ch.

Antibiotics are used in considerable amounts for the treatment of human infections and in veterinary medicine. Many of these substances end up in the aquatic environment, often unchanged, through natural excreta or improper disposal. The presence of antibiotics in the environment may contribute to increase resistance of microbes to some antibiotics. The aim of this study is to determine the amount of antibiotics that reaches the aquatic environment through different exposure routes, and to look at the environmental fate of these substances to provide a basis for risk assessment. Macrolide and sulfonamide antibiotics were used as model compounds. The developed method includes solid phase extraction followed by separation and quantification by

LC-MS. Initial studies on waste water treatment plant effluents and lake water showed the presence of sulfamethoxazole, trimethoprim and some macrolide antibiotics up to concentrations of 60 ng/L.

Occurrence of antibiotics in surface and ground water near confined animal feeding operations and waste water treatment plants using radioimmunoassay and liquid chromatography/electrospray mass spectrometry. M. Meyer, D.W. Kolpin, J.E. Bumgarner, J.L. Varns and J.V. Daughtridge. U.S. Geological Survey, 3916 Sunset Ridge Rd., Raleigh, NC 27607.

Approximately half of the 50 million pounds of antibiotics produced in the United States are used for agriculture and half for human health. Recent studies in Europe indicate that pharmaceutical compounds are common contaminants in surface water. Radioimmunoassay tests developed for clinical and regulatory use were adapted to screen for multiple classes of antibiotics in liquid waste and surface-water. A tandem reverse phase/mixed mode solid-phase extraction and liquid chromatography/mass spectrometry method was used to analyze for 21 analytes from four classes of antibiotics. Initial results indicate that antibiotics are transported into surface and ground water in areas with animal feeding operations and wastewater-treatment plants.

Occurrence of pharmaceutical residues in sewage, river, ground and drinking water in Greece and Germany. Thomas Heberer[1], Britta Fuhrmann[1], Kathrin Schmidt-Bäumler[1], Despina Tsipi[2], Vivian Koutsouba[2] and Anastassia Hiskia[3]. [1]Institute of Food Chemistry, Technical University of Berlin, Gustav-Meyer-Allee 25, Sekr. TIB 4/3-1, Berlin, 13355, Germany, fax: ++49 30 314 72823, thomas.heberer@tu-berlin.de; [2]General Chemical State Laboratory, 16, An. Tsoha, Athens, 11521, Greece; [3]Institute of Physical Chemistry, NCSR Demokritos, Athens, 15310, Greece.

A number of pharmaceutical compounds used in human medical care are not removed in the municipal sewage purification plants. Thus, they are discharged as persistent contaminants into the aquatic environment. Due to their polar structures these residues are not significantly adsorbed in the subsoil and may leach into the ground water aquifers from the contaminated surface waters. Especially, in conurbation's such as Berlin (Germany) with high municipal sewage water outputs and low surface water flows there is a potential risk of drinking water contamination when ground water recharge is used in drinking water production. Our latest investigations presented here were carried out in 1998 and 1999 in terms of a German-Hellenic cooperation. In this project the occurrence of drug residues in the aquatic environment in Berlin and in different cities in Greece was investigated and compared. The results demonstrate the extent and variety of surface water contamination by drug residues discharged from municipal sewage treatment plants.

Occurrence of phenazone analgesics in landfill-leachate polluted groundwater. Marijan Ahel[1] and Ivana Jelicic[2]. [1]Center for Marine and Environmental Research, Rudjer Boskovic Institute, P.O. Box 1016, Bijenicka 54, Zagreb, 10000, Croatia, fax: +385-1-4680242, abel@rudjer.irb.hr; [2]Faculty of Food Technology and Biotechnology, University of Zagreb, Pierottijeva 6, Zagreb, 10000, Croatia.

Analgesics belong to the most popular pharmaceutical chemicals. A comprehensive study conducted at the main landfill of the city of Zagreb, Croatia, indicated that phenazone analgesics, including propyphenazone (4-(1-methylethyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one), aminopyrine (4-(dimethylamino)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) and antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) were among the most abundant contaminants. This paper focuses on the determination of propyphenazone, aminopyrine and antipyrine in landfill leachate and groundwater. All identifications were performed by gas chromatography/mass spectrometry operated in full scan mode, while quantitative determinations were carried out in single ion monitoring mode, The spatial distribution of analgesics in landfill leachate was rather heterogeneous but the most abundant analgesic, propyphenazone, was detected in all analysed samples. Aminopyrine and propyphenazone were detected at significant concentrations in adjacent groundwater aquifer (1 to 50 microgram per liter), indicating an efficient vertical transport through the unsaturated zone.

Occurrence and fate of synthetic musks in the aquatic system of urban areas: Polycyclic and nitro musks as environmental pollutants in surface waters, sediments and biota. Thomas Heberer and Anja These. Institute of Food Chemistry, Technical University of Berlin, Sekr. TIB 4/3-1, Gustav-Meyer-Allee 25, Berlin, 13355, Germany, fax: ++49 30 314 72 823, thomas.heberer@tu-berlin.de.

Nitro musks and polycyclic musks summarized as "synthetic musks" are widely used as fragrances in cosmetics, detergents and other products. In 1996, the global annual production of polycyclic musks alone was estimated at more than 5000 tons. Synthetic musks are not eliminated significantly in the municipal sewage treatment plants. Thus, in Europe residues of synthetic musks have been detected up to the µg/L-level in sewage effluents and surface water samples. Due to their low rates of biological and biochemical degradation and due to their high lipophilic character synthetic musks are found at high concentrations at the top of the aquatic food chain and they are also found at considerable concentrations in human adipose tissue and human mothers milk.

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Pharmaceuticals and Personal Care Products in the Environment — An Emerging Concern

Go to Morning Session

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Time	Paper
1:30 p.m.	**Drugs in municipal sewage effluent: Screening and biodegradation studies.** E. Möhle and J.W. Metzger
1:50 p.m.	**Behavior of selected pharmaceuticals during drinking water treatment.** F. Sacher, B. Haist-Gulde, H.J. Brauch, N. Zullei-Seibert, G. Preuß, M. Meisenheimer, H. Welsch and T.A. Ternes
2:10 p.m.	**Concerns about pharmaceuticals in water reuse and animal waste.** H. Bouwer
2:30 p.m.	Break
2:50 p.m.	**Iodinated x-ray contrast media in the aquatic environment — fate and effects.** T. Steger-Hartmann, R. Länge and H. Schweinfurth
3:10 p.m.	**Multidrug/multixenobiotic transporters and their significance with respect to environmental levels of pharmaceuticals and personal care products.** D. Epel, N. Eufemia and S. Clerte
3:30 p.m.	**Ecotoxicological evaluation of pharmaceuticals.** T. Knacker, J. Roembke
3:50 p.m.	**Regulatory oversight for the environmental risk assessment of human and animal health drugs.** R. Velagaleti and J. Robinson
4:10 p.m.	**Degradation and depletion of pharmaceutical chemicals in the environment.** R. Velagaleti and J. Robinson

ABSTRACTS

Drugs in municipal sewage effluent: Screening and biodegradation studies. Edda Möhle and Jörg W. Metzger. Water Quality and Solid Waste Management, Department of Hydrochemistry and Hydrobiology, Institute of Sanitary Engineering, University of Stuttgart, Bandtäle 2, Stuttgart, 70569, Germany, fax: 49-711-685-3769, Edda.Moehle@iswa.uni-stuttgart.de.

Several human pharmaceuticals are found in the secondary effluent of municipal sewage plants. To get information about the degree of elimination (adsorption or degradation) or different drugs in a municipal sewage plant, tests under aerobic conditions were performed. A batch reactor suspension of activated sludge containing single drugs or a mixture of several drugs at environmentally relevant concentrations was coupled on-line with HPLC-MS-MS. The concentrations of most of the examined drugs determined after 15 minutes were significantly lower than their initial concentrations. We attributed this 'fast elimination' primarily to the adsorption of the drugs on the activated sludge. Most of the examined compounds displayed this sole route of "elimination". In contrast, for some of the compounds, an additional subsequent slow decrease of concentration could be observed until concentrations <1% of the initial concentration were reached. We believe this effect resulted primarily from primary degradation.

Behavior of selected pharmaceuticals during drinking water treatment. Frank Sacher[1], Brigitte Haist-Gulde[1], Heinz-Jürgen Brauch[1], Ninette Zullei-Seibert[2], Gudrun Preuß[2], Martin Meisenheimer[3], Helfried Welsch[3] and Thomas A. Ternes3. [1]DVGW-Technologiezentrum Wasser, Karlsruher Strasse 84, Karlsruhe, 76139, Germany, fax: 49-721-9678-104, Sacher@tzw.de; [2]Institut für Wasserforschung GmbH Dortmund, Zum Kellerbach 46, Schwerte, 58239, Germany; [3]ESWE-Institut für Wasserforschung und Wassertechnologie, Söhnleinstrasse 158, Wiesbaden, 65201, Germany.

The occurrence of pharmaceuticals and their metabolites in German surface and ground waters has been established by a number of investigators. The behavior of these compounds during drinking water preparation is therefore of major interest to drinking water suppliers. We investigated the behavior of four pharmaceuticals known to frequently occur in German waters (such as the rivers Rhine or Elbe): diclofenac (antirheumatic), carbamazepine (antiepileptic), bezafibrate (lipid regulator), and clofibric acid (the active metabolite of three lipid regulators). We made a detailed study of their fates during different drinking water treatment steps. All four compounds were readily biodegraded using slow sand filtration. In contrast, flocculation by Fe(III)chloride was an ineffective treatment alternative. Ozonation removed carbamazepine and

diclofenac extremely fast. Bezafibrate and clofibric acid, however, were only eliminated to a limited extent using ozonation. While granular activated carbon (GAC) filtration was also very effective for removal of carbamazepine, diclofenac, and bezafibrate, its elimination of clofibric acid depended on the water quality and on the processing-time of the GAC.

Concerns about pharmaceuticals in water reuse and animal waste. Herman Bouwer. U.S. Water Conservation Laboratory, USDA-ARS, 4331 E. Broadway Rd, Phoenix, AZ 85040.

Pharmaceuticals in sewage effluent could find their way into groundwater via seepage from contaminated streams and lakes, artificial recharge with sewage effluent, or drainage or deep-percolation from fields irrigated with sewage effluent. The latter is the most serious because contaminant concentrations in the deep-percolation water can be a multiple of those in the irrigation water. Land disposal of animal manure could also introduce pharmaceuticals in surface water and in groundwater.

Iodinated x-ray contrast media in the aquatic environment — fate and effects. Thomas Steger-Hartmann, Reinhard Länge and Hermann Schweinfurth. Research Laboratories, Schering AG, Müllerstraße 178, Berlin, D-13342, Germany, fax: 49-30-4681-5091, thomas.stegerhartmann@schering.de.

Iodinated X-ray contrast media are introduced into the aquatic environment due to patient excretion after radiologic examinations. On the basis of the annual consumption the expected introduction concentration (EIC) of contrast media into the environment, i.e. the waste water concentration, can be calculated with 30µg/l for the U.S. The substances are not mineralized in sewage treatment plants. In aquatic model systems degradation was observed, which starts with side-chain cleavage, leading to even more hydrophilic compounds than the parent compound, which are further amenable to photodegradation. Besides low mammalian toxicity and extremely low oral bioavailability the parent compounds and the tested metabolites also show low short- and long-term toxicity to aquatic species (EC/LC_{50} > 1g/l). A final risk assessment will be presented and the necessity of mitigation procedures discussed.

Multidrug/multixenobiotic transporters and their significance with respect to environmental levels of pharmaceuticals and personal care products. David Epel, Nancy Eufemia and Sophie Clerte. Hopkins Marine Station of Stanford University, Pacific Grove, CA 93950, fax: 831-375-0793, depel@leland.stanford.edu.

Knowing the fate of pharmaceuticals and personal care products (PPCPs) in the environment requires knowledge of their availability to the cell. Cells do not passively take up environmental compounds, but possess mechanisms to exclude compounds

that on the basis of chemical structure would otherwise be permeable. A major mechanism excluding many chemicals from cells is via "drug transporters" — ATP-dependent "efflux" transporters that actively remove compounds from the cell. The prototype for this "first line of defense" are conserved proteins referred to as p-glycoprotein transporters. This talk will provide background information on these transporters and consider whether PPCPs are substrates. I will consider a confounding aspect of the protective effect of these transporters, which arises from the ability of many compounds, both natural and man-made, to alter the transport capacity of these proteins. If the PPCPs alter transport, then toxic compounds that normally are excluded from cells might enter the cytoplasm and there wreak havoc.

Ecotoxicological evaluation of pharmaceuticals. Thomas Knacker and J. Roembke. ECT Oekotoxikologie GmbH Böttgerstr. 2-14, Flörscheim a.M, D-65439, Germany, th-knacker@ect.de.

An Environmental Risk Assessment (ERA) scheme for medicinal products is presented. The scheme, based on strategies developed by the European Union for pesticides and for new and existing chemicals, is compared and contrasted with guidelines set forth by the U.S. (FDA) and EU (Committee for Veterinary Medicinal Products) for the assessment of potential risks to the environment posed by pharmaceuticals. Emphasis is placed on the criteria that might be used to identify those products for which an extended ERA is considered necessary. Some details are given as to which tests should be applied to evaluate ecotoxicological fate and effects of medicinal products — chemicals that are designed to exhibit specific biological effects (e.g. antibiotics, synthetic steroids). Examples are shown for ERA of medicinal products for which the available literature data are sufficient to demonstrate the usefulness of the proposed ERA scheme. Finally, areas for further research are identified.

Regulatory oversight for the environmental risk assessment of human and animal health drugs. Ranga Velagaleti[1] and Joseph Robinson[2]. [1]ABC Laboratories, Inc, 7200 E. ABC Lane, Columbia, MO 65202, fax: 573-443-9090, Velagaleti@aol.com; [2]Pharmacia & Upjohn, Inc, 7000 Portage Road, Kalamazoo, MI 49001-0199.

The assessment of environmental risk of the manufacture, use, and distribution of human and animal health drugs is required in the United States under the National Environmental Policy Act (NEPA). The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) published guidance for Environmental Risk Assessment (ERA) of human Drugs and Biologics to meet the NEPA requirements. The European Agency for the Evaluation of Medicinal Products (EMEA) has under the auspices of European Commission published guidance document for human health drugs in a draft form. The Committee for the Veterinary Medicinal Products (CVMP) of the EMEA published final guidance for the ERA of the veterinary medicinal products. We will discuss the basic elements of these guidance

documents, including the studies and documentation required for preparing ERA for various regulatory agencies as a part of the approval of human and animal health drugs.

Degradation and depletion of pharmaceutical chemicals in the environment.

Ranga Velagaleti[1] and Joseph Robinson[2]. [1]ABC Laboratories, Inc, 7200 E. ABC Lane, Columbia, MO 65202, fax: 573-443-9090, Velagaleti@aol.com; [2]Pharmacia & Upjohn, Inc, 7000 Portage Road, Kalamazoo, MI 49001-0199.

Various regulatory agencies around the world have set limits for environmental exposures that will trigger "action" or "no action" scenarios for providing an "Enviromental Risk Assessment" (ERA) or an exclusion from an ERA, respectively. In this presentation, we will illustrate various scenarios, where human and animal health drugs could result in exposure to various environmental matrices (e.g., soils and surface waters). The potential degradation and depletion mechanisms specific to each of these environmental matrices will be discussed along with a discussion on the potential for decline of drug substance residues. Hydrolysis and photolysis (chemical transformation), and biodegradation (mineralization and biotransformation) are the common mechanisms of degradation and depletion of pharmaceutical residues. The degradation and depletion as well as dilution in surface water or soil are presented as mechanisms of drug residue depletion in the environment leading to potential zero risk exposures for many pharmaceutical drugs.